



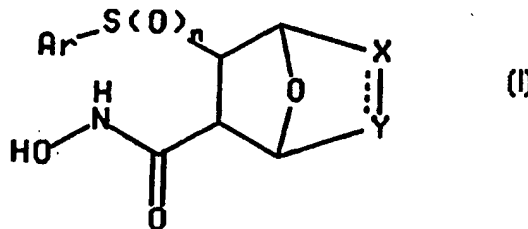
## INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification <sup>6</sup> : <b>C07D 493/08, A61K 31/34</b>	<b>A1</b>	(11) International Publication Number: <b>WO 98/30566</b> (43) International Publication Date: 16 July 1998 (16.07.98)
<p>(21) International Application Number: PCT/IB97/01582</p> <p>(22) International Filing Date: 18 December 1997 (18.12.97)</p> <p>(30) Priority Data: 60/034,535 6 January 1997 (06.01.97) US</p> <p>(71) Applicant (for all designated States except US): PFIZER INC. [US/US]; 235 East 42nd Street, New York, NY 10017 (US).</p> <p>(72) Inventors; and (75) Inventors/Applicants (for US only): BURGESS, Laurence, Edward [US/US]; 5617 Slick Rock Court, Boulder, CO 80301 (US). RIZZI, James, Patrick [US/US]; 7180 Longview Drive, Niwot, CO 80503 (US).</p> <p>(74) Agents: SPIEGEL, Allen, J. et al.; Pfizer Inc., 235 East 42nd Street, New York, NY 10017 (US).</p>		<p>(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).</p> <p>Published With international search report.</p>

(54) Title: CYCLIC SULFONE DERIVATIVES

## (57) Abstract

A compound of formula (I), wherein n, X, Y and Ar are as defined herein, useful in the treatment of a condition selected from the group consisting of arthritis, cancer, tissue ulceration, macular degeneration, restenosis, periodontal disease, epidermolysis bullosa, scleritis, and other diseases characterized by matrix metalloproteinase activity, AIDS, sepsis, septic shock and other diseases involving the production of TNF. In addition, the compounds of the present invention may be used in combination therapy with standard non-steroidal anti-inflammatory drugs (NSAID'S) and analgesics, and in combination with cytotoxic drugs such as adriamycin, daunomycin, cis-platinum, etoposide, taxol, taxotere and other alkaloids, such as vincristine, in the treatment of cancer.



**FOR THE PURPOSES OF INFORMATION ONLY**

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
AM	Armenia	FI	Finland	LT	Lithuania	SK	Slovakia
AT	Austria	FR	France	LU	Luxembourg	SN	Senegal
AU	Australia	GA	Gabon	LV	Latvia	SZ	Swaziland
AZ	Azerbaijan	GB	United Kingdom	MC	Monaco	TD	Chad
BA	Bosnia and Herzegovina	GE	Georgia	MD	Republic of Moldova	TG	Togo
BB	Barbados	GH	Ghana	MG	Madagascar	TJ	Tajikistan
BE	Belgium	GN	Guinea	MK	The former Yugoslav	TM	Turkmenistan
BF	Burkina Faso	GR	Greece		Republic of Macedonia	TR	Turkey
BG	Bulgaria	HU	Hungary	ML	Mali	TT	Trinidad and Tobago
BJ	Benin	IE	Ireland	MN	Mongolia	UA	Ukraine
BR	Brazil	IL	Israel	MR	Mauritania	UG	Uganda
BY	Belarus	IS	Iceland	MW	Malawi	US	United States of America
CA	Canada	IT	Italy	MX	Mexico	UZ	Uzbekistan
CF	Central African Republic	JP	Japan	NE	Niger	VN	Viet Nam
CG	Congo	KE	Kenya	NL	Netherlands	YU	Yugoslavia
CH	Switzerland	KG	Kyrgyzstan	NO	Norway	ZW	Zimbabwe
CI	Côte d'Ivoire	KP	Democratic People's	NZ	New Zealand		
CM	Cameroon		Republic of Korea	PL	Poland		
CN	China	KR	Republic of Korea	PT	Portugal		
CU	Cuba	KZ	Kazakhstan	RO	Romania		
CZ	Czech Republic	LC	Saint Lucia	RU	Russian Federation		
DE	Germany	LI	Liechtenstein	SD	Sudan		
DK	Denmark	LK	Sri Lanka	SE	Sweden		
EE	Estonia	LR	Liberia	SG	Singapore		

-1-

5

CYCLIC SULFONE DERIVATIVESBackground of the Invention

The present invention relates to cyclic sulfone derivatives which are inhibitors of matrix metalloproteinases or the production of tumor necrosis factor (TNF) and as such are useful in the treatment of a condition selected from the group consisting of arthritis, cancer, tissue ulceration, restenosis, periodontal disease, epidermolysis bullosa, scleritis and other diseases characterized by matrix metalloproteinase activity, AIDS, sepsis, septic shock and other diseases involving the production of TNF. In addition, the compounds of the present invention may be used in combination therapy with standard non-steroidal anti-inflammatory drugs (hereinafter NSAID'S) and analgesics for the treatment of arthritis, and in combination with cytotoxic drugs such as adriamycin, daunomycin, cis-platinum, etoposide, taxol, taxotere and alkaloids, such as vincristine, in the treatment of cancer.

This invention also relates to a method of using such compounds in the treatment of the above diseases in mammals, especially humans, and to pharmaceutical compositions useful therefor.

There are a number of enzymes which effect the breakdown of structural proteins and which are structurally related metalloproteases. Matrix-degrading metalloproteinases, such as gelatinase, stromelysin and collagenase, are involved in tissue matrix degradation (e.g. collagen collapse) and have been implicated in many pathological conditions involving abnormal connective tissue and basement membrane matrix metabolism, such as arthritis (e.g. osteoarthritis and rheumatoid arthritis), tissue ulceration (e.g. corneal, epidermal and gastric ulceration), abnormal wound healing, periodontal disease, bone disease (e.g. Paget's disease and osteoporosis), tumor metastasis or invasion, as well as HIV-infection (J. Leuk. Biol., 52 (2): 244-248, 1992).

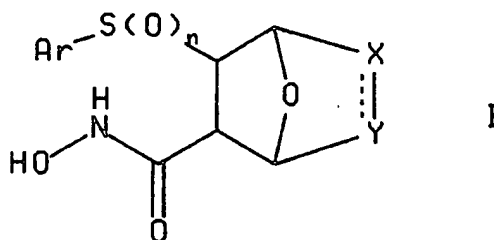
Tumor necrosis factor is recognized to be involved in many infectious and auto-immune diseases (W. Fiers, FEBS Letters, 1991, 285, 199). Furthermore, it has been shown that TNF is the prime mediator of the inflammatory response seen in sepsis and septic shock (C.E. Spooner et al., Clinical Immunology and Immunopathology, 1992, 62 S11).

-2-

Summary of the Invention

The present invention relates to a compound of the formula

5



or a pharmaceutically acceptable salt thereof, wherein the broken line represents an  
10 optional double bond;

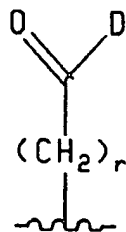
n is 0, 1 or 2;

X and Y are each independently CR<sup>1</sup> wherein R<sup>1</sup> is hydrogen, (C<sub>1</sub>-C<sub>6</sub>)alkyl optionally substituted by (C<sub>1</sub>-C<sub>6</sub>)alkylamino, (C<sub>1</sub>-C<sub>6</sub>)alkylthio, (C<sub>1</sub>-C<sub>6</sub>)alkoxy, trifluoromethyl, (C<sub>6</sub>-C<sub>10</sub>)aryl, (C<sub>5</sub>-C<sub>9</sub>)heteroaryl, (C<sub>6</sub>-C<sub>10</sub>)arylamino, (C<sub>6</sub>-C<sub>10</sub>)arylthio, (C<sub>6</sub>-C<sub>10</sub>)aryloxy, (C<sub>5</sub>-C<sub>9</sub>)heteroarylamino, (C<sub>5</sub>-C<sub>9</sub>)heteroarylthio, (C<sub>5</sub>-C<sub>9</sub>)heteroaryloxy, (C<sub>6</sub>-C<sub>10</sub>)aryl(C<sub>6</sub>-C<sub>10</sub>)aryl, (C<sub>3</sub>-C<sub>6</sub>)cycloalkyl, hydroxy(C<sub>1</sub>-C<sub>6</sub>)alkyl, (C<sub>1</sub>-C<sub>6</sub>)alkyl(hydroxymethylene), piperazinyl, (C<sub>6</sub>-C<sub>10</sub>)aryl(C<sub>1</sub>-C<sub>6</sub>)alkoxy, (C<sub>5</sub>-C<sub>9</sub>)heteroaryl(C<sub>1</sub>-C<sub>6</sub>)alkoxy, (C<sub>1</sub>-C<sub>6</sub>)acylamino, (C<sub>1</sub>-C<sub>6</sub>)acylthio, (C<sub>1</sub>-C<sub>6</sub>)acyloxy, (C<sub>1</sub>-C<sub>6</sub>)alkylsulfinyl, (C<sub>6</sub>-C<sub>10</sub>)arylsulfinyl, (C<sub>1</sub>-C<sub>6</sub>)alkylsulfonyl, (C<sub>6</sub>-C<sub>10</sub>)arylsulfonyl, amino, (C<sub>1</sub>-C<sub>6</sub>)alkylamino or  
20 ((C<sub>1</sub>-C<sub>6</sub>)alkyl)<sub>2</sub>amino; trifluoromethyl, (C<sub>1</sub>-C<sub>6</sub>)alkyl (difluoromethylene), (C<sub>1</sub>C<sub>3</sub>)alkyl(difluoromethylene)(C<sub>1</sub>-C<sub>3</sub>)alkyl, (C<sub>6</sub>-C<sub>10</sub>)aryl, (C<sub>5</sub>-C<sub>9</sub>)heteroaryl, (C<sub>3</sub>-C<sub>6</sub>)cycloalkyl, (C<sub>1</sub>-C<sub>6</sub>)alkyl-(hydroxymethylene), R<sup>3</sup>(C<sub>1</sub>-C<sub>6</sub>)alkyl wherein R<sup>3</sup> is (C<sub>1</sub>-C<sub>6</sub>)acylpiperazino, (C<sub>6</sub>-C<sub>10</sub>)arylpiperazino, (C<sub>5</sub>-C<sub>9</sub>)heteroarylpiperazino, (C<sub>1</sub>-C<sub>6</sub>)alkylpiperazino, (C<sub>6</sub>-C<sub>10</sub>)aryl(C<sub>1</sub>-C<sub>6</sub>)alkylpiperazino, (C<sub>5</sub>-C<sub>9</sub>)heteroaryl(C<sub>1</sub>-C<sub>6</sub>)alkylpiperazino, morpholino, thiomorpholino, piperidino, pyrrolidino, piperidyl, (C<sub>1</sub>-C<sub>6</sub>)alkylpiperidyl, (C<sub>6</sub>-C<sub>10</sub>)arylpiperidyl, (C<sub>5</sub>-C<sub>9</sub>)heteroarylpiperidyl, (C<sub>1</sub>-C<sub>6</sub>)alkylpiperidyl(C<sub>1</sub>-C<sub>6</sub>)alkyl, (C<sub>6</sub>-C<sub>10</sub>)arylpiperidyl(C<sub>1</sub>-C<sub>6</sub>)alkyl, (C<sub>5</sub>-C<sub>9</sub>)heteroarylpiperidyl(C<sub>1</sub>-C<sub>6</sub>)alkyl or (C<sub>1</sub>-C<sub>6</sub>)acylpiperidyl;

30

or a group of the formula

-3-



5

wherein r is 0 to 6;

- Dis hydroxy, (C<sub>1</sub>-C<sub>6</sub>)alkoxy, piperidyl, (C<sub>1</sub>-C<sub>6</sub>)alkylpiperidyl, (C<sub>6</sub>-C<sub>10</sub>)arylpiperidyl, (C<sub>5</sub>-C<sub>9</sub>)heteroarylpiperidyl, (C<sub>1</sub>-C<sub>6</sub>)acylpiperidyl or NR<sup>4</sup>R<sup>5</sup> wherein R<sup>4</sup> and R<sup>5</sup> are each
- 10 independently selected from the group consisting of hydrogen, (C<sub>1</sub>-C<sub>6</sub>)alkyl optionally substituted by (C<sub>1</sub>-C<sub>6</sub>)alkylpiperidyl, (C<sub>6</sub>-C<sub>10</sub>)arylpiperidyl, (C<sub>5</sub>-C<sub>9</sub>)heteroarylpiperidyl, (C<sub>6</sub>-C<sub>10</sub>)aryl, (C<sub>5</sub>-C<sub>9</sub>)heteroaryl, (C<sub>6</sub>-C<sub>10</sub>)aryl(C<sub>6</sub>-C<sub>10</sub>)aryl or (C<sub>3</sub>-C<sub>6</sub>)cycloalkyl; (C<sub>6</sub>-C<sub>10</sub>)aryl, (C<sub>5</sub>-C<sub>9</sub>)heteroaryl, (C<sub>6</sub>-C<sub>10</sub>)aryl(C<sub>6</sub>-C<sub>10</sub>)aryl, (C<sub>3</sub>-C<sub>6</sub>)cycloalkyl, R<sup>6</sup>(C<sub>2</sub>-C<sub>6</sub>)alkyl, (C<sub>1</sub>-C<sub>5</sub>)alkyl(CHR<sup>6</sup>)(C<sub>1</sub>-C<sub>6</sub>)alkyl wherein R<sup>6</sup> is hydroxy, (C<sub>1</sub>-C<sub>6</sub>)acyloxy, (C<sub>1</sub>-C<sub>6</sub>)alkoxy,
- 15 piperazino, (C<sub>1</sub>-C<sub>6</sub>)acylamino, (C<sub>1</sub>-C<sub>6</sub>)alkylthio, (C<sub>6</sub>-C<sub>10</sub>)arylthio, (C<sub>1</sub>-C<sub>6</sub>)alkylsulfinyl, (C<sub>6</sub>-C<sub>10</sub>)arylsulfinyl, (C<sub>1</sub>-C<sub>6</sub>)alkylsulfoxyl, (C<sub>6</sub>-C<sub>10</sub>)arylsulfoxyl, amino, (C<sub>1</sub>-C<sub>6</sub>)alkylamino, ((C<sub>1</sub>-C<sub>6</sub>)alkyl)<sub>2</sub>amino, (C<sub>1</sub>-C<sub>6</sub>)acylpiperazino, (C<sub>1</sub>-C<sub>6</sub>)alkylpiperazino, (C<sub>6</sub>-C<sub>10</sub>)aryl(C<sub>1</sub>-C<sub>6</sub>)alkylpiperazino, (C<sub>5</sub>-C<sub>9</sub>)heteroaryl(C<sub>1</sub>-C<sub>6</sub>)alkylpiperazino, morpholino, thiomorpholino, piperidino or pyrrolidino; R<sup>7</sup>(C<sub>1</sub>-C<sub>6</sub>)alkyl, (C<sub>1</sub>-C<sub>5</sub>)alkyl(CHR<sup>7</sup>)(C<sub>1</sub>-C<sub>6</sub>)alkyl wherein R<sup>7</sup> is
- 20 piperidyl or (C<sub>1</sub>-C<sub>6</sub>)alkylpiperidyl; and CH(R<sup>8</sup>)COR<sup>9</sup> wherein R<sup>8</sup> is hydrogen, (C<sub>1</sub>-C<sub>6</sub>)alkyl, (C<sub>6</sub>-C<sub>10</sub>)aryl(C<sub>1</sub>-C<sub>6</sub>)alkyl, (C<sub>5</sub>-C<sub>9</sub>)heteroaryl(C<sub>1</sub>-C<sub>6</sub>)alkyl, (C<sub>1</sub>-C<sub>6</sub>)alkylthio(C<sub>1</sub>-C<sub>6</sub>)alkyl, (C<sub>6</sub>-C<sub>10</sub>)arylthio(C<sub>1</sub>-C<sub>6</sub>)alkyl, (C<sub>1</sub>-C<sub>6</sub>)alkylsulfinyl(C<sub>1</sub>-C<sub>6</sub>)alkyl, (C<sub>6</sub>-C<sub>10</sub>)arylsulfinyl(C<sub>1</sub>-C<sub>6</sub>)alkyl, (C<sub>1</sub>-C<sub>6</sub>)alkylsulfonyl(C<sub>1</sub>-C<sub>6</sub>)alkyl, (C<sub>6</sub>-C<sub>10</sub>)arylsulfonyl(C<sub>1</sub>-C<sub>6</sub>)alkyl, hydroxy(C<sub>1</sub>-C<sub>6</sub>)alkyl, amino(C<sub>1</sub>-C<sub>6</sub>)alkyl, (C<sub>1</sub>-C<sub>6</sub>)alkylamino(C<sub>1</sub>-C<sub>6</sub>)alkyl, ((C<sub>1</sub>-C<sub>6</sub>)alkylamino)<sub>2</sub>(C<sub>1</sub>-C<sub>6</sub>)alkyl,
- 25 R<sup>10</sup>R<sup>11</sup>NCO(C<sub>1</sub>-C<sub>6</sub>)alkyl or R<sup>10</sup>OCO(C<sub>1</sub>-C<sub>6</sub>)alkyl wherein R<sup>10</sup> and R<sup>11</sup> are each independently selected from the group consisting of hydrogen, (C<sub>1</sub>-C<sub>6</sub>)alkyl, (C<sub>6</sub>-C<sub>10</sub>)aryl(C<sub>1</sub>-C<sub>6</sub>)alkyl and (C<sub>5</sub>-C<sub>9</sub>)heteroaryl(C<sub>1</sub>-C<sub>6</sub>)alkyl; and R<sup>9</sup> is R<sup>12</sup>O or R<sup>12</sup>R<sup>13</sup>N wherein R<sup>12</sup> and R<sup>13</sup> are each independently selected from the group consisting of hydrogen, (C<sub>1</sub>-C<sub>6</sub>)alkyl, (C<sub>6</sub>-C<sub>10</sub>)aryl(C<sub>1</sub>-C<sub>6</sub>)alkyl and (C<sub>5</sub>-C<sub>9</sub>)heteroaryl(C<sub>1</sub>-C<sub>6</sub>)alkyl; and
- 30 Ar is (C<sub>1</sub>-C<sub>6</sub>)alkyl, (C<sub>6</sub>-C<sub>10</sub>)aryl, (C<sub>6</sub>-C<sub>10</sub>)aryloxy(C<sub>6</sub>-C<sub>10</sub>)aryl, (C<sub>6</sub>-C<sub>10</sub>)aryl(C<sub>6</sub>-C<sub>10</sub>)aryl, (C<sub>6</sub>-C<sub>10</sub>)aryl(C<sub>6</sub>-C<sub>10</sub>)aryl(C<sub>1</sub>-C<sub>6</sub>)alkyl, (C<sub>6</sub>-C<sub>10</sub>)aryloxy(C<sub>5</sub>-C<sub>9</sub>)heteroaryl, (C<sub>5</sub>-C<sub>9</sub>)heteroaryl, (C<sub>1</sub>-C<sub>6</sub>)alkyl(C<sub>6</sub>-C<sub>10</sub>)aryl, (C<sub>1</sub>-C<sub>6</sub>)alkoxy(C<sub>6</sub>-C<sub>10</sub>)aryl, (C<sub>6</sub>-C<sub>10</sub>)aryl(C<sub>1</sub>-C<sub>6</sub>)alkoxy(C<sub>6</sub>-C<sub>10</sub>)aryl, (C<sub>6</sub>-C<sub>10</sub>)aryl(C<sub>1</sub>-C<sub>6</sub>)alkoxy(C<sub>1</sub>-C<sub>6</sub>)alkyl, (C<sub>5</sub>-C<sub>9</sub>)heteroaryloxy(C<sub>6</sub>-

(C<sub>10</sub>)aryl, (C<sub>1</sub>-C<sub>6</sub>)alkyl(C<sub>5</sub>-C<sub>9</sub>)heteroaryl, (C<sub>1</sub>-C<sub>6</sub>)alkoxy(C<sub>5</sub>-C<sub>9</sub>)heteroaryl, (C<sub>6</sub>-C<sub>10</sub>)aryl(C<sub>1</sub>-C<sub>6</sub>)alkoxy(C<sub>5</sub>-C<sub>9</sub>)heteroaryl, (C<sub>5</sub>-C<sub>9</sub>)heteroaryloxy(C<sub>5</sub>-C<sub>9</sub>)heteroaryl, (C<sub>6</sub>-C<sub>10</sub>)aryloxy(C<sub>1</sub>-C<sub>6</sub>)alkyl, (C<sub>5</sub>-C<sub>9</sub>)heteroaryloxy(C<sub>1</sub>-C<sub>6</sub>)alkyl, (C<sub>1</sub>-C<sub>6</sub>)alkyl(C<sub>6</sub>-C<sub>10</sub>)aryloxy(C<sub>6</sub>-C<sub>10</sub>)aryl, (C<sub>1</sub>-C<sub>6</sub>)alkyl(C<sub>5</sub>-C<sub>9</sub>)heteroaryloxy(C<sub>6</sub>-C<sub>10</sub>)aryl, (C<sub>1</sub>-C<sub>6</sub>)alkyl(C<sub>6</sub>-C<sub>10</sub>)aryloxy(C<sub>5</sub>-C<sub>9</sub>)heteroaryl, 5 (C<sub>1</sub>-C<sub>6</sub>)alkoxy(C<sub>6</sub>-C<sub>10</sub>)aryloxy(C<sub>6</sub>-C<sub>10</sub>)aryl, (C<sub>1</sub>-C<sub>6</sub>)alkoxy(C<sub>5</sub>-C<sub>9</sub>)heteroaryloxy(C<sub>6</sub>-C<sub>10</sub>)aryl or (C<sub>1</sub>-C<sub>6</sub>)alkoxy(C<sub>6</sub>-C<sub>10</sub>)aryloxy(C<sub>5</sub>-C<sub>9</sub>)heteroaryl wherein each aryl group is optionally substituted by fluoro, chloro, bromo, (C<sub>1</sub>-C<sub>6</sub>)alkyl, (C<sub>1</sub>-C<sub>6</sub>)alkoxy or perfluoro(C<sub>1</sub>-C<sub>3</sub>)alkyl.

The term "alkyl", as used herein, unless otherwise indicated, includes saturated monovalent hydrocarbon radicals having straight, branched or cyclic moieties or 10 combinations thereof.

The term "alkoxy", as used herein, includes alkyl-O groups wherein "alkyl" is defined above.

The term "aryl", as used herein, unless otherwise indicated, includes an organic radical derived from an aromatic hydrocarbon by removal of one hydrogen, such as 15 phenyl or naphthyl, optionally substituted by 1 to 3 substituents independently selected from the group consisting of fluoro, chloro, cyano, nitro, trifluoromethyl, (C<sub>1</sub>-C<sub>6</sub>)alkoxy, (C<sub>6</sub>-C<sub>10</sub>)aryloxy, trifluoromethoxy, difluoromethoxy and (C<sub>1</sub>-C<sub>6</sub>)alkyl.

The term "heteroaryl", as used herein, unless otherwise indicated, includes an organic radical derived from an aromatic heterocyclic compound by removal of one 20 hydrogen, such as pyridyl, furyl, pyrrolyl, thienyl, isothiazolyl, imidazolyl, benzimidazolyl, tetrazolyl, pyrazinyl, pyrimidyl, quinolyl, isoquinolyl, benzofuryl, isobenzofuryl, benzothienyl, pyrazolyl, indolyl, isoindolyl, purinyl, carbazolyl, isoxazolyl, thiazolyl, oxazolyl, benzthiazolyl or benzoxazolyl, optionally substituted by 1 to 2 substituents independently selected from the group consisting of fluoro, chloro, trifluoromethyl, (C<sub>1</sub>-C<sub>6</sub>)alkoxy, (C<sub>6</sub>-C<sub>10</sub>)aryloxy, trifluoromethoxy, difluoromethoxy and (C<sub>1</sub>-C<sub>6</sub>)alkyl. 25

The term "acyl", as used herein, unless otherwise indicated, includes a radical of the general formula RCO wherein R is alkyl, alkoxy, aryl, arylalkyl or arylalkyloxy and the terms "alkyl" or "aryl" are as defined above.

The term "acyloxy", as used herein, includes acyl-O groups wherein "acyl" is 30 defined above.

Preferred compounds of formula I include those wherein n is 2.

Other preferred compounds of formula I include those wherein X and Y are both CR<sup>1</sup> wherein R<sup>1</sup> is hydrogen.

Other preferred compounds of formula I include those wherein Ar is (C<sub>1</sub>-C<sub>6</sub>)alkoxy(C<sub>6</sub>-C<sub>10</sub>)aryl, (C<sub>6</sub>-C<sub>10</sub>)aryl, (C<sub>1</sub>-C<sub>6</sub>)alkoxy(C<sub>6</sub>-C<sub>10</sub>)aryl, 4-fluorophenoxy(C<sub>6</sub>-C<sub>10</sub>)aryl, 4-fluorobenzoyloxy(C<sub>6</sub>-C<sub>10</sub>)aryl or (C<sub>1</sub>-C<sub>6</sub>)alkyl(C<sub>6</sub>-C<sub>10</sub>)aryloxy(C<sub>6</sub>-C<sub>10</sub>)aryl.

More preferred compounds of formula I include those wherein n is 2, X and Y are both CR<sup>1</sup> wherein R<sup>1</sup> is hydrogen and Ar is (C<sub>1</sub>-C<sub>6</sub>)alkoxy(C<sub>6</sub>-C<sub>10</sub>)aryl, (C<sub>6</sub>-C<sub>10</sub>)aryl, (C<sub>1</sub>-C<sub>6</sub>)alkoxy(C<sub>6</sub>-C<sub>10</sub>)aryl, 4-fluorophenoxy(C<sub>6</sub>-C<sub>10</sub>)aryl, 4-fluorobenzoyloxy(C<sub>6</sub>-C<sub>10</sub>)aryl or (C<sub>1</sub>-C<sub>6</sub>)alkyl(C<sub>6</sub>-C<sub>10</sub>)aryloxy(C<sub>6</sub>-C<sub>10</sub>)aryl.

The present invention also relates to a pharmaceutical composition for (a) the treatment of a condition selected from the group consisting of arthritis, cancer, synergy with cytotoxic anticancer agents, tissue ulceration, macular degeneration, restenosis, periodontal disease, epidermolysis bullosa, scleritis, in combination with standard NSAID'S and analgesics and other diseases characterized by matrix metalloproteinase activity, AIDS, sepsis, septic shock and other diseases involving the production of tumor necrosis factor (TNF) or (b) the inhibition of matrix metalloproteinases or the production of tumor necrosis factor (TNF) in a mammal, including a human, comprising an amount of a compound of formula I or a pharmaceutically acceptable salt thereof effective in such treatments and a pharmaceutically acceptable carrier.

The present invention also relates to a method for the inhibition of (a) matrix metalloproteinases or (b) the production of tumor necrosis factor (TNF) in a mammal, including a human, comprising administering to said mammal an effective amount of a compound of formula I or a pharmaceutically acceptable salt thereof.

The present invention also relates to a method for treating a condition selected from the group consisting of arthritis, cancer, tissue ulceration, macular degeneration, restenosis, periodontal disease, epidermolysis bullosa, scleritis, compounds of formula I may be used in combination with standard NSAID'S and analgesics and in combination with cytotoxic anticancer agents, and other diseases characterized by matrix metalloproteinase activity, AIDS, sepsis, septic shock and other diseases involving the production of tumor necrosis factor (TNF) in a mammal, including a human, comprising administering to said mammal an amount of a compound of formula I or a pharmaceutically acceptable salt thereof effective in treating such a condition.

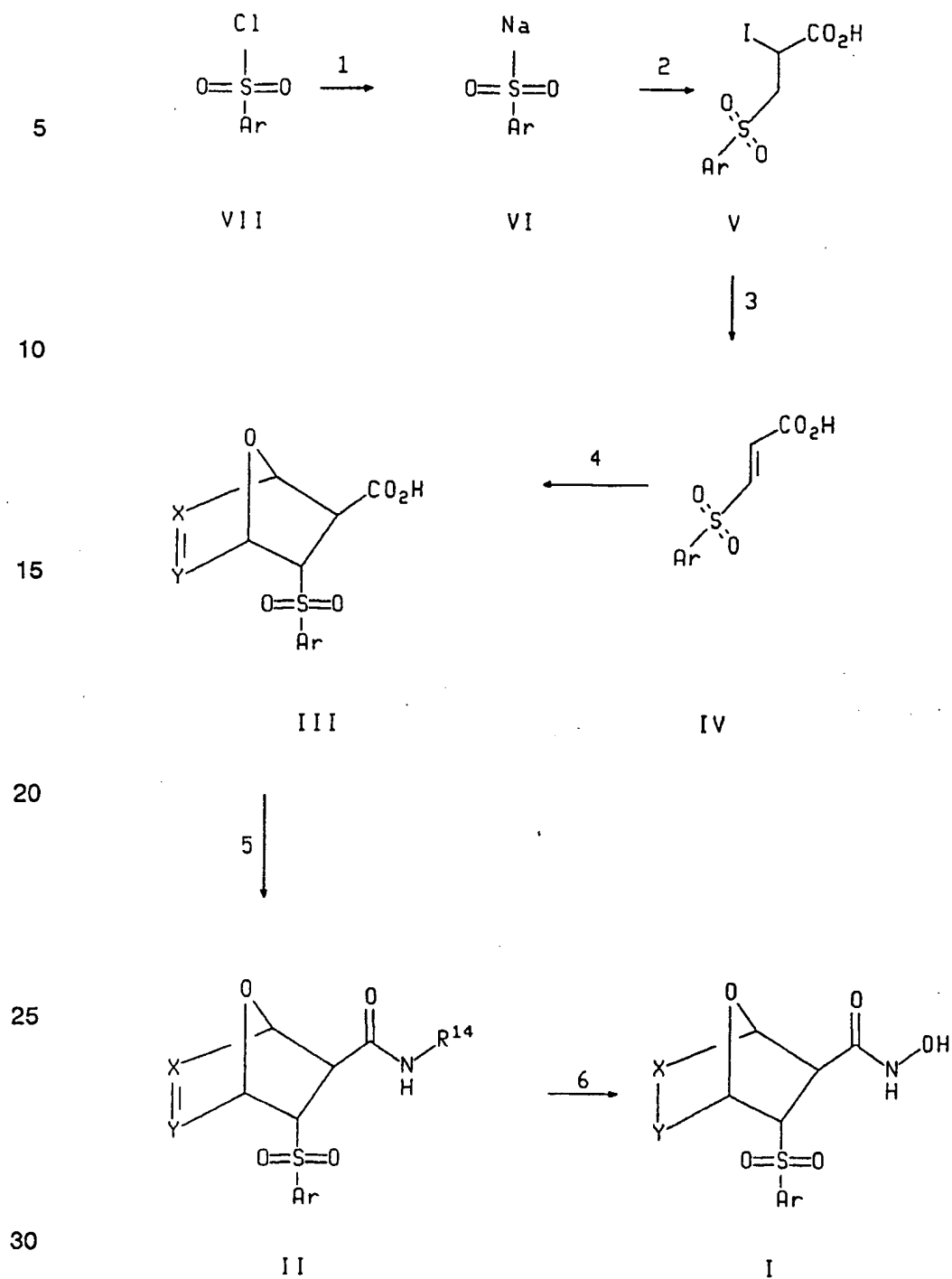
Detailed Description of the Invention

The following reaction Schemes illustrate the preparation of the compounds of the present invention. Unless otherwise indicated X, Y and Ar in the reaction Schemes and the discussion that follow are defined as above.



-7-

**SCHEME 1**



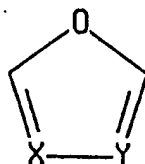
-8-

In reaction 1 of Scheme 1, the aryl sulfonyl chloride compound of formula VII is converted to the corresponding sodium aryl sulfonate compound of formula VI by reacting VII with sodium iodine in the presence of a polar aprotic solvent, such as acetone, under inert atmosphere. The reaction mixture is stirred, at room temperature, for a time period between about 12 hours to about 18 hours, preferably about 15 hours.

In reaction 2 of Scheme 1, the compound of formula VI is converted to the corresponding 2-iodo-3-(aryl) sulfonyl propionic acid compound of formula V by reacting VI with acrylic acid and iodine in the presence of a polar aprotic solvent, such as methylene chloride. The reaction mixture is stirred under inert atmosphere, at room temperature, for a time period between about 12 hours to about 3.5 days, preferably about 3 days.

In reaction 3 of Scheme 1, the compound of formula V is converted to the corresponding (E)-3-(aryl)sulfonyl-prop-2-enoic acid compound of formula IV by treating V with a base, such as triethylamine, in a polar aprotic solvent, such as methylene chloride, under inert atmosphere. The reaction is stirred, at room temperature, for a time period between about 10 hours to about 24 hours, preferably about 12 hours.

In reaction 4 of Scheme 1, the compound of formula IV is converted to the corresponding carboxylic acid compound of formula III by heating IV with an excess amount of a compound of the formula



to reflux in the presence of a polar aprotic solvent, such as toluene, for a time period between about 24 hours to about 56 hours, preferably about 48 hours.

In reaction 5 of Scheme 1, the compound of formula III is converted to the corresponding N-(R<sup>14</sup>)-carboxamide compound of formula II, wherein R<sup>14</sup> is O-substituted oxy, such as O-benzylhydroxy or trimethylsilyl ethylhydroxy by reacting III with an activating agent, such as dimethylaminopyridine/dicyclohexylcarbodiimide, and an O-substituted hydroxylamine, such as benzylhydroxylamine hydrochloride or O-trimethyl-silylethylhydroxylamine, in the presence of a polar aprotic solvent, such as methylene chloride, under inert atmosphere. The reaction mixture is stirred, at room

temperature, for a time period between about 15 hours to about 25 hours, preferably about 20 hours.

In reaction 6 of Scheme 1, the compound of formula II is converted to the corresponding hydroxamic acid compound of formula I by (1) treating II with hydrogen in the presence of a catalyst, such as 5% palladium on barium sulfate, and a polar aprotic solvent, such as methanol, (2) treating II with trifluoroacetic acid or boron trifluoride diethyl etherate in a polar aprotic solvent, such as methylene chloride, or (3) treating II with tetrabutyl ammonium fluoride in a polar aprotic solution, such as tetrahydrofuran. The reaction mixture is stirred for a time period between about 2 hours to about 4 hours, preferably about 3 hours.

Pharmaceutically acceptable salts of the acidic compounds of the invention are salts formed with bases, namely cationic salts such as alkali and alkaline earth metal salts, such as sodium, lithium, potassium, calcium, magnesium, as well as ammonium salts, such as ammonium, trimethyl-ammonium, diethylammonium, and tris-(hydroxymethyl)-methylammonium salts.

Similarly acid addition salts, such as of mineral acids, organic carboxylic and organic sulfonic acids e.g. hydrochloric acid, methanesulfonic acid, maleic acid, are also possible provided a basic group, such as pyridyl, constitutes part of the structure.

The ability of the compounds of formula I or their pharmaceutically acceptable salts (hereinafter also referred to as the compounds of the present invention) to inhibit matrix metalloproteinases or the production of tumor necrosis factor (TNF) and, consequently, demonstrate their effectiveness for treating diseases characterized by matrix metalloproteinase or the production of tumor necrosis factor is shown by the following *in vitro* assay tests.

#### Biological Assay

##### Inhibition of Human Collagenase (MMP-1)

Human recombinant collagenase is activated with trypsin using the following ratio: 10  $\mu$ g trypsin per 100  $\mu$ g of collagenase. The trypsin and collagenase are incubated at room temperature for 10 minutes then a five fold excess (50  $\mu$ g/10  $\mu$ g trypsin) of soybean trypsin inhibitor is added.

10 mM stock solutions of inhibitors are made up in dimethyl sulfoxide and then diluted using the following Scheme:

10 mM  $\longrightarrow$  120  $\mu$ M  $\longrightarrow$  12  $\mu$ M  $\longrightarrow$  1.2  $\mu$ M  $\longrightarrow$  0.12  $\mu$ M

-10-

Twenty-five microliters of each concentration is then added in triplicate to appropriate wells of a 96 well microfluor plate. The final concentration of inhibitor will be a 1:4 dilution after addition of enzyme and substrate. Positive controls (enzyme, no inhibitor) are set up in wells D1-D6 and blanks (no enzyme, no inhibitors) are set in  
5 wells D7-D12.

Collagenase is diluted to 400 ng/ml and 25  $\mu$ l is then added to appropriate wells of the microfluor plate. Final concentration of collagenase in the assay is 100 ng/ml.

Substrate (DNP-Pro-Gly-Cys(Me)-His-Ala-Lys(NMA)-NH<sub>2</sub>) is made as a 5 mM stock in dimethyl sulfoxide and then diluted to 20  $\mu$ M in assay buffer. The assay is  
10 initiated by the addition of 50  $\mu$ l substrate per well of the microfluor plate to give a final concentration of 10  $\mu$ M.

Fluorescence readings (360 nm excitation, 460 nm emission) were taken at time 0 and then at 20 minute intervals. The assay is conducted at room temperature with a typical assay time of 3 hours.

15 Fluorescence vs time is then plotted for both the blank and collagenase containing samples (data from triplicate determinations is averaged). A time point that provides a good signal (the blank) and that is on a linear part of the curve (usually around 120 minutes) is chosen to determine IC<sub>50</sub> values. The zero time is used as a blank for each compound at each concentration and these values are subtracted from  
20 the 120 minute data. Data is plotted as inhibitor concentration vs % control (inhibitor fluorescence divided by fluorescence of collagenase alone x 100). IC<sub>50</sub>'s are determined from the concentration of inhibitor that gives a signal that is 50% of the control.

If IC<sub>50</sub>'s are reported to be <0.03  $\mu$ M then the inhibitors are assayed at  
25 concentrations of 0.3  $\mu$ M, 0.03  $\mu$ M, 0.03  $\mu$ M and 0.003  $\mu$ M.

#### Inhibition of Gelatinase (MMP-2)

Inhibition of gelatinase activity is assayed using the Dnp-Pro-Gly-Cys(Me)-His-Ala-Lys(NMA)-NH<sub>2</sub> substrate (10  $\mu$ M) under the same conditions as inhibition of human collagenase (MMP-1).

30 72kD gelatinase is activated with 1 mM APMA (p-aminophenyl mercuric acetate) for 15 hours at 4°C and is diluted to give a final concentration in the assay of 100 mg/ml. Inhibitors are diluted as for inhibition of human collagenase (MMP-1) to give

-11-

final concentrations in the assay of 30  $\mu\text{M}$ , 3  $\mu\text{M}$ , 0.3  $\mu\text{M}$  and 0.03  $\mu\text{M}$ . Each concentration is done in triplicate.

Fluorescence readings (360 nm excitation, 460 emission) are taken at time zero and then at 20 minutes intervals for 4 hours.

- 5         $\text{IC}_{50}$ 's are determined as per inhibition of human collagenase (MMP-1). If  $\text{IC}_{50}$ 's are reported to be less than 0.03  $\mu\text{M}$ , then the inhibitors are assayed at final concentrations of 0.3  $\mu\text{M}$ , 0.03  $\mu\text{M}$ , 0.003  $\mu\text{M}$  and 0.0003  $\mu\text{M}$ .

Inhibition of Stromelysin Activity (MMP-3)

- 10        Inhibition of stromelysin activity is based on a modified spectrophotometric assay described by Weingarten and Feder (Weingarten, H. and Feder, J., Spectrophotometric Assay for Vertebrate Collagenase, Anal. Biochem. 147, 437-440 (1985)). Hydrolysis of the thio peptolide substrate [Ac-Pro-Leu-Gly-SCH[CH<sub>2</sub>CH(CH<sub>3</sub>)<sub>2</sub>]CO-Leu-Gly-OC<sub>2</sub>H<sub>5</sub>] yields a mercaptan fragment that can be monitored in the presence of Ellman's reagent.

- 15        Human recombinant prostromelysin is activated with trypsin using a ratio of 1  $\mu\text{l}$  of a 10 mg/ml trypsin stock per 26  $\mu\text{g}$  of stromelysin. The trypsin and stromelysin are incubated at 37°C for 15 minutes followed by 10  $\mu\text{l}$  of 10 mg/ml soybean trypsin inhibitor for 10 minutes at 37°C for 10 minutes at 37°C to quench trypsin activity.

- 20        Assays are conducted in a total volume of 250  $\mu\text{l}$  of assay buffer (200 mM sodium chloride, 50 mM MES, and 10 mM calcium chloride, pH 6.0) in 96-well microliter plates. Activated stromelysin is diluted in assay buffer to 25  $\mu\text{g}/\text{ml}$ . Ellman's reagent (3-Carboxy-4-nitrophenyl disulfide) is made as a 1M stock in dimethyl formamide and diluted to 5 mM in assay buffer with 50  $\mu\text{l}$  per well yielding at 1 mM final concentration.

- 25        10 mM stock solutions of inhibitors are made in dimethyl sulfoxide and diluted serially in assay buffer such that addition of 50  $\mu\text{L}$  to the appropriate wells yields final concentrations of 3  $\mu\text{M}$ , 0.3  $\mu\text{M}$ , 0.003  $\mu\text{M}$ , and 0.0003  $\mu\text{M}$ . All conditions are completed in triplicate.

- 30        A 300 mM dimethyl sulfoxide stock solution of the peptide substrate is diluted to 15 mM in assay buffer and the assay is initiated by addition of 50  $\mu\text{l}$  to each well to give a final concentration of 3 mM substrate. Blanks consist of the peptide substrate and Ellman's reagent without the enzyme. Product formation was monitored at 405 nm with a Molecular Devices UVmax plate reader.

$\text{IC}_{50}$  values were determined in the same manner as for collagenase.

### Inhibition of MMP-13

Human recombinant MMP-13 is activated with 2mM APMA (p-aminophenyl mercuric acetate) for 1.5 hours, at 37°C and is diluted to 400 mg/ml in assay buffer (50 mM Tris, pH 7.5, 200 mM sodium chloride, 5mM calcium chloride, 20μM zinc chloride, 0.02% brij). Twenty-five microliters of diluted enzyme is added per well of a 96 well microfluor plate. The enzyme is then diluted in a 1:4 ratio in the assay by the addition of inhibitor and substrate to give a final concentration in the assay of 100 mg/ml.

10 mM stock solutions of inhibitors are made up in dimethyl sulfoxide and then diluted in assay buffer as per the inhibitor dilution scheme for inhibition of human collagenase (MMP-1): Twenty-five microliters of each concentration is added in triplicate to the microfluor plate. The final concentrations in the assay are 30 μM, 3μM, 0.3 μM, and 0.03 μM.

Substrate (Dnp-Pro-Gly-Cys(Me)-His-Ala-Lys(NMA)-NH<sub>2</sub>) is prepared as for inhibition of human collagenase (MMP-1) and 50 μl is added to each well to give a final assay concentration of 10 μM. Fluorescence readings (360 nM excitation; 450 emission) are taken at time 0 and every 5 minutes for 1 hour.

Positive controls consist of enzyme and substrate with no inhibitor and blanks consist of substrate only.

IC<sub>50</sub>'s are determined as per inhibition of human collagenase (MMP-1). If IC<sub>50</sub>'s are reported to be less than 0.03 μM, inhibitors are then assayed at final concentrations of 0.3 μM, 0.03 μM, 0.003 μM and 0.0003 μM.

### Inhibition of TNF Production

The ability of the compounds or the pharmaceutically acceptable salts thereof to inhibit the production of TNF and, consequently, demonstrate their effectiveness for treating diseases involving the production of TNF is shown by the following in vitro assay:

Human mononuclear cells were isolated from anti-coagulated human blood using a one-step Ficoll-hypaque separation technique. (2) The mononuclear cells were washed three times in Hanks balanced salt solution (HBSS) with divalent cations and resuspended to a density of  $2 \times 10^6$  /ml in HBSS containing 1% BSA. Differential counts determined using the Abbott Cell Dyn 3500 analyzer indicated that monocytes ranged from 17 to 24% of the total cells in these preparations.

-13-

180 $\mu$ l of the cell suspension was aliquoted into flat bottom 96 well plates (Costar). Additions of compounds and LPS (100ng/ml final concentration) gave a final volume of 200 $\mu$ l. All conditions were performed in triplicate. After a four hour incubation at 37°C in an humidified CO<sub>2</sub> incubator, plates were removed and  
5 centrifuged (10 minutes at approximately 250 x g) and the supernatants removed and assayed for TNF $\alpha$  using the R&D ELISA Kit.

For administration to humans for the inhibition of matrix metalloproteinases or the production of tumor necrosis factor, a variety of conventional routes may be used including orally, parenterally and topically. In general, the active compound will be  
10 administered orally or parenterally at dosages between about 0.1 and 25 mg/kg body weight of the subject to be treated per day, preferably from about 0.3 to 5 mg/kg. However, some variation in dosage will necessarily occur depending on the condition of the subject being treated. The person responsible for administration will, in any event, determine the appropriate dose for the individual subject.

15 The compounds of the present invention can be administered in a wide variety of different dosage forms, in general, the compounds of this invention are present in such dosage forms at concentration levels ranging from about 5.0% to about 70% by weight.

For oral administration, tablets containing various excipients such as  
20 microcrystalline cellulose, sodium citrate, calcium carbonate, dicalcium phosphate and glycine may be employed along with various disintegrants such as starch (and preferably corn, potato or tapioca starch), alginic acid and certain complex silicates, together with granulation binders like polyvinylpyrrolidone, sucrose, gelatin and acacia. Additionally, lubricating agents such as magnesium stearate, sodium lauryl sulfate and  
25 talc are often very useful for tableting purposes. Solid compositions of a similar type may also be employed as fillers in gelatin capsules; preferred materials in this connection also include lactose or milk sugar as well as high molecular weight polyethylene glycols. When aqueous suspensions and/or elixirs are desired for oral  
30 administration, the active ingredient may be combined with various sweetening or flavoring agents, coloring matter or dyes, and emulsifying and/or suspending agents as well, together with such diluents as water, ethanol, propylene glycol, glycerin and various like combinations thereof. In the case of animals, they are advantageously

-14-

contained in an animal feed or drinking water in a concentration of 5-5000 ppm, preferably 25 to 500 ppm.

For parenteral administration (intramuscular, intraperitoneal, subcutaneous and intravenous use) a sterile injectable solution of the active ingredient is usually prepared.

- 5 Solutions of a therapeutic compound of the present invention in either sesame or peanut oil or in aqueous propylene glycol may be employed. The aqueous solutions should be suitably adjusted and buffered, preferably at a pH of greater than 8, if necessary and the liquid diluent first rendered isotonic. These aqueous solutions are suitable for intravenous injection purposes. The oily solutions are suitable for
- 10 intraarticular, intramuscular and subcutaneous injection purposes. The preparation of all these solutions under sterile conditions is readily accomplished by standard pharmaceutical techniques well known to those skilled in the art. In the case of animals, compounds can be administered intramuscularly or subcutaneously at dosage levels of about 0.1 to 50 mg/kg/day, advantageously 0.2 to 10 mg/kg/day given in a
- 15 single dose or up to 3 divided doses.

Additionally, it is possible to administer the compounds of the present invention topically, e.g., when treating inflammatory conditions of the skin and this may be done by way of creams, jellies, gels, pastes, and ointments, in accordance with standard pharmaceutical practice.

- 20 The present invention is illustrated by the following examples, but is not limited to the details thereof.

#### Example 1

3-(4-Methoxyphenylsulfonyl-7-oxabicyclo[2.2.1]heptane-2-carboxylic acid hydroxyamide

- 25 (a) Sodium iodide (21.76 grams, 145.2 mmol) and 4-methoxybenzenesulfonyl chloride (10.0 grams, 48.39 mmol) were combined in dry acetone (dried over  $\text{MgSO}_4$  and filtered) (200 ml) and stirred at room temperature overnight. Collected fine white solids via suction filtration. Dried on high vacuum giving 9.11 grams of sodium 4-methoxybenzenesulfinate as a pale yellow fine powder (97% yield).
- 30 (b) Added water (0.85 grams, .85 ml) followed by th acrylic acid (3.42 grams, 3.25 ml), then  $\text{I}_2$  (12.04 grams, 47.41 mmol) to a slurry of sodium 4-methoxybenzenesulfinate (9.11 grams, 46.94 mmol) in methylene chloride (150 ml). Added more methylene chloride (100 ml) so slurry could stir. Stirred at room



-15-

temperature for week nd. Washed reaction solution with 1N  $\text{Na}_2\text{S}_2\text{O}_3$  (aq) (3 x 150 ml) until organic layer was colorless. Washed organic layer with brine. Dried ( $\text{MgSO}_4$ ), filtered and concentrated in vacuo, to give 4.23 grams (25%) of crude 2-iodo-3-(4-methoxyphenylsulfonyl)propionic acid.

5 (c) 2-Iodo-3-(4-methoxyphenylsulfonyl)propionic acid (4.23 grams, 11.43 mmol) and  $\text{Et}_3\text{N}$  (3.22 ml, 2.34 grams, 23.09 mmol) were combined in methylene chloride (150 ml) and stirred overnight at room temperature. The reaction mixture was diluted with 1N hydrochloric acid(aq) (100 ml). The separated aqueous layer was extracted with  $\text{Et}_2\text{O}$  (2x). The dried ( $\text{MgSO}_4$ ) combined organics were then filtered and  
10 concentrated in vacuo to give 2.58 grams of crude product. This was filtered, the filtrate concentrated and the residue taken up in methanol, filtered and the filtrate concentrated to give 1.87 grams of crude product. This was taken up in hot methylene chloride. Fine crystals crashed out. Decanted filtrate. Washed crystals methylene chloride (2 x 1 ml) (decanted washings). Dried crystals on high vac to give .396 grams  
15 of 3-(4-Methoxyphenylsulfonyl)propenoic acid as a pale yellow solid (m.p.:  $123^\circ - 128.5^\circ\text{C}$ ). The filtrate was concentrated to give 1.42 grams of yellow solid which was flash chromatographed (60%  $\text{EtOAc}$ /hexane/2%/HOAc/.5% methanol) to give 1.42 grams of 3-(4-Methoxyphenylsulfonyl)propenoic acid. A second chromatography (40%  $\text{EtOAc}$ /hexane/2%/HOAc/.5% methanol) gave .568 grams of pure 3-(4-  
20 Methoxyphenylsulfonyl)propenoic acid.

(d) 3-(4-Methoxyphenylsulfonyl)propenoic acid (200 mgs), excess furan (5.0 ml), and dry toluene (5.0 ml) were combined and warmed to  $55^\circ\text{C}$  (at which time starting material went into solution) for overnight. The cooled reaction was concentrated in vacuo to a tan solid which was a mixture of starting material and  
25 product. The material was taken up in toluene (5 ml) and furan (10 ml) and heated to  $69^\circ\text{C}$  overnight. The cooled reaction mixture was concentrated in vacuo to give 251 mgs of crude 3-(4-Methoxyphenylsulfonyl)-7-oxabicyclo[2.2.1]hept-5-ene-2-carboxylic acid as a dark tan solid.

(e) Added the O-benzylhydroxylamine $\cdot$ hydrochloric acid (.387 grams, 2.43  
30 mmol) to a stirred solution of 3-(4-methoxy-phenylsulfonyl-7-oxabicyclo[2.2.1]h pt-5-ene-2-carboxylic acid in methylene chloride (5 ml). Add d 4-dimethylaminopyridin (.306 grams, 2.51 mmol) and stirred approximately one-half hour (until solids dissolved), then added the 1,3-dicyclohexylcarbodiimide (.250 grams, 1.21 mmol) and stirred at

-16-

room temperature overnight. The reaction was filtered through a pad of Celite and the filtrate concentrated in vacuo to give 1.06 grams of 3-(4-Methoxyphenylsulfonyl)-7-oxabicyclo[2.2.1]heptane-2-carboxylic acid benzyloxyamide. Took this up in methanol and decanted filtrate from fine needle crystals. Concentration of filtrate gave .82 grams of 3-(4-Methoxyphenylsulfonyl)-7-oxabicyclo[2.2.1]heptane-2-carboxylic acid benzyloxyamide.

(f) Added 5% palladium/barium sulfate (.80 grams) to crude 3-(4-methoxyphenylsulfonyl)-7-oxa-bicyclo[2.2.1]hept-5-ene-2-carboxylic acid benzyloxy amide (0.82 grams) in 30 ml methanol and hydrogenated at 45 psi at room temperature on a Parr Shaker for 4 hours. Filtered the reaction through a pad of Celite and concentrated the filtrate in vacuo. <sup>1</sup>H-NMR of the residue shows only the double bond has been removed. The residue was flash chromatographed (50% EtOAc/hexane) to give .126 grams of intermediate. To this was added 5% palladium/barium sulfate (.126 grams) in methanol (30 ml) and hydrogenation was continued on a Parr Shaker at 45 psi at room temperature for 1 3/4 hours. Filtered the reaction through a pad of Celite and concentrated the filtrate to give .101 grams of crude 3-(4-Methoxyphenylsulfonyl)-7-oxabicyclo[2.2.1]heptane-2-carboxylic acid hydroxyamide. Flash chromatographed (70/30/8/1) (EtOAc/hexane/methanol/HOAc) to give 77.1 mg of 3-(4-Methoxyphenylsulfonyl)-7-oxabicyclo[2.2.1]heptane-2-carboxylic acid hydroxyamide. <sup>1</sup>H-NMR (CD<sub>3</sub>OD)  $\delta$  1.6 (2H, m), 1.8 (2H, m), 3.11 (1H, t), 3.82 (1H, d), 3.88 (3H, s), 4.63 (1H, t), 4.91 (1H, d), 7.12 (2H, d), 7.80 (2H, d); HRMS M<sup>+</sup>+H<sup>+</sup>, Calc'd: 328.0855, Found: 328.0872.

### Example 2

#### 3-(4-Phenoxyphenylsulfonyl)-7-oxabicyclo[2.2.1]heptane-2-carboxylic acid hydroxyamide

(a) 3-(4-Phenoxyphenylsulfonyl)propenoic acid prepared from 4-phenoxyphenylsulfonyl chloride and acrylic acid as described in Example 1 steps A and B was flash chromatographed (60/40/1.5/.5 - EtOAc/hexane/HOAc/methanol) to give 1.12 grams of product as an off-white solid. This was crystallized from EtOAc/hexane (3:1) to give .61 grams of pure product as fine white crystals.

(b) To 3-(4-phenoxyphenylsulfonyl)propenoic acid (250 mgs, .82 mmol) in toluene (5.0 ml) (starting material insoluble in toluene at room temperature) was added furan (10 ml) and the mixture heated to gentle reflux approximately 70°C. After

-17-

approximately on -half hour the reaction mixture was a solution. After 18 hours of reflux TLC of the milky white solution shows starting material to be consumed. The reaction mixture was cooled and the white precipitate collected via suction filtration and washed with toluene (2 x 1 ml). Dissolved solids in hot methanol and concentrated in vacuo to give .267 grams of 2-(4-Phenoxyphenylsulfonyl-7-oxabicyclo[2.2.1]hept-5-ene-2-carboxylic acid as a white crystalline solid.

(c) 3-(4-Phenoxyphenylsulfonyl-7-oxabicyclo[2.2.1]hept-5-ene-2-carboxylic acid (.243 grams, 0.65 mmol) was hydrogenated on a Parr Shaker over 5% palladium/barium sulfate (.125 grams) in methanol (30 ml) at room temperature at 45 psi for 3 hours. The reaction was filtered through a pad of Celite and the filtrate concentrated in vacuo to give .216 grams of 3-(4-Phenoxyphenylsulfonyl)-7-oxabicyclo[2.2.1]heptane-2-carboxylic acid.

(d) Added the o-benzylhydroxylamine<sup>o</sup>hydrochloric acid (.28 grams, 1.73 mmol) to the 3-(4-phenoxyphenylsulfonyl)-7-oxabicyclo[2.2.1]heptane-2-carboxylic acid (.216 grams, .58 mmol) dissolved in  $\text{CHCl}_3$  with heating to dissolve it. Then the 4-dimethylaminopyridine (.22 grams, 1.79 mmol) was added and the mixture stirred until complete dissolution occurred approximately 5 minutes. Then the 1,3-dicyclohexylcarbodiimide (.18 grams, .87 mmol) was added. After 18 hours stirring at room temperature the reaction was concentrated in vacuo to give 1.05 grams of crude product. Flash chromatography (40% EtOAc/hexane/2%/HOAc/.5% methanol) gave .32 grams of impure product. Flash chromatography (40% EtOAc/hexane) gave .212 grams (75%) of pure 3-(4-Phenoxyphenylsulfonyl)-7-oxabicyclo[2.2.1]heptane-2-carboxylic acid benzyloxy amide as a snow white foamy solid.

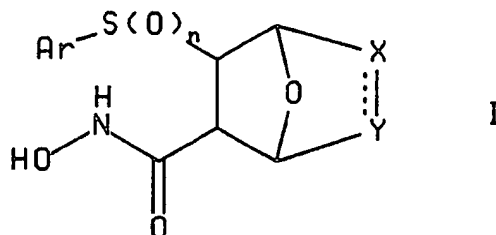
(e) Combined 3-(4-phenoxyphenylsulfonyl)-7-oxabicyclo[2.2.1]heptane-2-carboxylic acid (.21 grams, .438 mmol) 5% palladium/barium sulfate (.11 grams) in methanol (20 ml) and hydrogenated on a Parr Shaker at room temperature at 45 psi for 1 3/4 hours. The reaction mixture was filtered and concentrated in vacuo to give .175 grams of 3-(4-Phenoxyphenylsulfonyl-7-oxabicyclo[2.2.1]heptane-2-carboxylic acid hydroxyamide as a snow white foamy solid, m.p. 88.9° - 92.9°C.  $^1\text{H-NMR}$  ( $\text{CD}_3\text{OD}$ )  $\delta$  2.5-2.7 (2H, m), 2.7-2.9 (2H, m), 3.11 (1H, t), 3.84 (1H, d), 4.64 (1H, t), 4.94 (1H, d), 7.10 (4H, d), 7.23 (1H, t), 7.44 (2, t), 7.82 (2H, d); mass spec  $\text{M}^+ + \text{NH}_4^+$  407. HRMS  $\text{M}^+ + \text{H}^+$ , Calc'd: 390.1011, Found: 390.1022.

-18-

PRODUCT CLAIMS

1. A compound of the formula

5



or a pharmaceutically acceptable salt thereof, wherein the broken line represents an  
10 optional double bond;

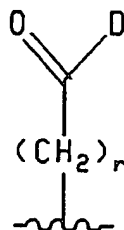
n is 0, 1 or 2;

X and Y are each independently CR<sup>1</sup> wherein R<sup>1</sup> is hydrogen, (C<sub>1</sub>-C<sub>6</sub>)alkyl optionally substituted by (C<sub>1</sub>-C<sub>6</sub>)alkylamino, (C<sub>1</sub>-C<sub>6</sub>)alkylthio, (C<sub>1</sub>-C<sub>6</sub>)alkoxy, trifluoromethyl, (C<sub>6</sub>-C<sub>10</sub>)aryl, (C<sub>5</sub>-C<sub>9</sub>)heteroaryl, (C<sub>6</sub>-C<sub>10</sub>)arylamino, (C<sub>6</sub>-C<sub>10</sub>)arylthio, (C<sub>6</sub>-  
15 C<sub>10</sub>)aryloxy, (C<sub>5</sub>-C<sub>9</sub>)heteroarylamino, (C<sub>5</sub>-C<sub>9</sub>)heteroarylthio, (C<sub>5</sub>-C<sub>9</sub>)heteroaryloxy, (C<sub>6</sub>-C<sub>10</sub>)aryl(C<sub>6</sub>-C<sub>10</sub>)aryl, (C<sub>3</sub>-C<sub>6</sub>)cycloalkyl, hydroxy(C<sub>1</sub>-C<sub>6</sub>)alkyl, (C<sub>1</sub>-C<sub>6</sub>)alkyl(hydroxymethylene), piperazinyl, (C<sub>6</sub>-C<sub>10</sub>)aryl(C<sub>1</sub>-C<sub>6</sub>)alkoxy, (C<sub>5</sub>-C<sub>9</sub>)heteroaryl(C<sub>1</sub>-C<sub>6</sub>)alkoxy, (C<sub>1</sub>-C<sub>6</sub>)acylamino, (C<sub>1</sub>-C<sub>6</sub>)acylthio, (C<sub>1</sub>-C<sub>6</sub>)acyloxy, (C<sub>1</sub>-C<sub>6</sub>)alkylsulfinyl, (C<sub>6</sub>-C<sub>10</sub>)arylsulfinyl, (C<sub>1</sub>-C<sub>6</sub>)alkylsulfonyl, (C<sub>6</sub>-C<sub>10</sub>)arylsulfonyl, amino, (C<sub>1</sub>-C<sub>6</sub>)alkylamino or  
20 ((C<sub>1</sub>-C<sub>6</sub>)alkyl)<sub>2</sub>amino; trifluoromethyl, (C<sub>1</sub>-C<sub>6</sub>)alkyl (difluoromethylene), (C<sub>1</sub>C<sub>3</sub>)alkyl(difluoromethylene)(C<sub>1</sub>-C<sub>3</sub>)alkyl, (C<sub>6</sub>-C<sub>10</sub>)aryl, (C<sub>5</sub>-C<sub>9</sub>)heteroaryl, (C<sub>3</sub>-C<sub>6</sub>)cycloalkyl, (C<sub>1</sub>-C<sub>6</sub>)alkyl-(hydroxymethylene), R<sup>3</sup>(C<sub>1</sub>-C<sub>6</sub>)alkyl wherein R<sup>3</sup> is (C<sub>1</sub>-C<sub>6</sub>)acylpiperazino, (C<sub>6</sub>-C<sub>10</sub>)arylpiperazino, (C<sub>5</sub>-C<sub>9</sub>)heteroarylpiperazino, (C<sub>1</sub>-C<sub>6</sub>)alkylpiperazino, (C<sub>6</sub>-C<sub>10</sub>)aryl(C<sub>1</sub>-C<sub>6</sub>)alkylpiperazino, (C<sub>5</sub>-C<sub>9</sub>)heteroaryl(C<sub>1</sub>-  
25 C<sub>6</sub>)alkylpiperazino, morpholino, thiomorpholino, piperidino, pyrrolidino, piperidyl, (C<sub>1</sub>-C<sub>6</sub>)alkylpiperidyl, (C<sub>6</sub>-C<sub>10</sub>)arylpiperidyl, (C<sub>5</sub>-C<sub>9</sub>)heteroarylpiperidyl, (C<sub>1</sub>-C<sub>6</sub>)alkylpiperidyl(C<sub>1</sub>-C<sub>6</sub>)alkyl, (C<sub>6</sub>-C<sub>10</sub>)arylpiperidyl(C<sub>1</sub>-C<sub>6</sub>)alkyl, (C<sub>5</sub>-C<sub>9</sub>)heteroarylpiperidyl(C<sub>1</sub>-C<sub>6</sub>)alkyl or (C<sub>1</sub>-C<sub>6</sub>)acylpiperidyl;

or a group of the formula

30

-19-



5

wherein  $r$  is 0 to 6;

- $D$  is hydroxy,  $(C_1-C_6)$ alkoxy, piperidyl,  $(C_1-C_6)$ alkylpiperidyl,  $(C_6-C_{10})$ aryl piperidyl,  $(C_5-C_9)$ heteroaryl piperidyl,  $(C_1-C_6)$ acylpiperidyl or  $NR^4R^5$  wherein  $R^4$  and  $R^5$  are each
- 10 independently selected from the group consisting of hydrogen,  $(C_1-C_6)$ alkyl optionally substituted by  $(C_1-C_6)$ alkylpiperidyl,  $(C_6-C_{10})$ aryl piperidyl,  $(C_5-C_9)$ heteroaryl piperidyl,  $(C_6-C_{10})$ aryl,  $(C_5-C_9)$ heteroaryl,  $(C_6-C_{10})$ aryl  $(C_6-C_{10})$ aryl or  $(C_3-C_6)$ cycloalkyl;  $(C_6-C_{10})$ aryl,  $(C_5-C_9)$ heteroaryl,  $(C_6-C_{10})$ aryl  $(C_6-C_{10})$ aryl,  $(C_3-C_6)$ cycloalkyl,  $R^6(C_2-C_6)$ alkyl,  $(C_1-C_5)$ alkyl  $(CHR^6)(C_1-C_6)$ alkyl wherein  $R^6$  is hydroxy,  $(C_1-C_6)$ acyloxy,  $(C_1-C_6)$ alkoxy,
- 15 piperazino,  $(C_1-C_6)$ acylamino,  $(C_1-C_6)$ alkylthio,  $(C_6-C_{10})$ arylthio,  $(C_1-C_6)$ alkylsulfinyl,  $(C_6-C_{10})$ arylsulfinyl,  $(C_1-C_6)$ alkylsulfoxyl,  $(C_6-C_{10})$ arylsulfoxyl, amino,  $(C_1-C_6)$ alkylamino,  $((C_1-C_6)$ alkyl)<sub>2</sub>amino,  $(C_1-C_6)$ acylpiperazino,  $(C_1-C_6)$ alkylpiperazino,  $(C_6-C_{10})$ aryl  $(C_1-C_6)$ alkylpiperazino,  $(C_5-C_9)$ heteroaryl  $(C_1-C_6)$ alkylpiperazino, morpholino, thiomorpholino, piperidino or pyrrolidino;  $R^7(C_1-C_6)$ alkyl,  $(C_1-C_5)$ alkyl  $(CHR^7)(C_1-C_6)$ alkyl wherein  $R^7$  is
- 20 piperidyl or  $(C_1-C_6)$ alkylpiperidyl; and  $CH(R^8)COR^9$  wherein  $R^8$  is hydrogen,  $(C_1-C_6)$ alkyl,  $(C_6-C_{10})$ aryl  $(C_1-C_6)$ alkyl,  $(C_5-C_9)$ heteroaryl  $(C_1-C_6)$ alkyl,  $(C_1-C_6)$ alkylthio  $(C_1-C_6)$ alkyl,  $(C_6-C_{10})$ arylthio  $(C_1-C_6)$ alkyl,  $(C_1-C_6)$ alkylsulfinyl  $(C_1-C_6)$ alkyl,  $(C_6-C_{10})$ arylsulfinyl  $(C_1-C_6)$ alkyl,  $(C_1-C_6)$ alkylsulfonyl  $(C_1-C_6)$ alkyl,  $(C_6-C_{10})$ arylsulfonyl  $(C_1-C_6)$ alkyl, hydroxy  $(C_1-C_6)$ alkyl, amino  $(C_1-C_6)$ alkyl,  $(C_1-C_6)$ alkylamino  $(C_1-C_6)$ alkyl,  $((C_1-C_6)$ alkylamino)<sub>2</sub>  $(C_1-C_6)$ alkyl,
- 25  $R^{10}R^{11}NCO(C_1-C_6)$ alkyl or  $R^{10}OCO(C_1-C_6)$ alkyl wherein  $R^{10}$  and  $R^{11}$  are each independently selected from the group consisting of hydrogen,  $(C_1-C_6)$ alkyl,  $(C_6-C_{10})$ aryl  $(C_1-C_6)$ alkyl and  $(C_5-C_9)$ heteroaryl  $(C_1-C_6)$ alkyl; and  $R^9$  is  $R^{12}O$  or  $R^{12}R^{13}N$  wherein  $R^{12}$  and  $R^{13}$  are each independently selected from the group consisting of hydrogen,  $(C_1-C_6)$ alkyl,  $(C_6-C_{10})$ aryl  $(C_1-C_6)$ alkyl and  $(C_5-C_9)$ heteroaryl  $(C_1-C_6)$ alkyl; and
- 30  $Ar$  is  $(C_1-C_6)$ alkyl,  $(C_6-C_{10})$ aryl,  $(C_6-C_{10})$ aryloxy  $(C_6-C_{10})$ aryl,  $(C_6-C_{10})$ aryl  $(C_6-C_{10})$ aryl,  $(C_6-C_{10})$ aryl  $(C_6-C_{10})$ aryl  $(C_1-C_6)$ alkyl,  $(C_6-C_{10})$ aryloxy  $(C_5-C_9)$ heteroaryl,  $(C_5-C_9)$ heteroaryl,  $(C_1-C_6)$ alkyl  $(C_6-C_{10})$ aryl,  $(C_1-C_6)$ alkoxy  $(C_6-C_{10})$ aryl,  $(C_6-C_{10})$ aryl  $(C_1-C_6)$ alkoxy  $(C_6-C_{10})$ aryl,  $(C_6-C_{10})$ aryl  $(C_1-C_6)$ alkoxy  $(C_1-C_6)$ alkyl,  $(C_5-C_9)$ heteroaryloxy  $(C_6-$

-20-

$C_{10}$ )aryl,  $(C_1-C_6)$ alkyl( $C_5-C_9$ )heteroaryl,  $(C_1-C_6)$ alkoxy( $C_5-C_9$ )heteroaryl,  $(C_6-C_{10})$ aryl( $C_1-C_6$ )alkoxy( $C_5-C_9$ )heteroaryl,  $(C_5-C_9)$ heteroaryloxy( $C_5-C_9$ )heteroaryl,  $(C_6-C_{10})$ aryloxy( $C_1-C_6$ )alkyl,  $(C_5-C_9)$ heteroaryloxy( $C_1-C_6$ )alkyl,  $(C_1-C_6)$ alkyl( $C_6-C_{10})$ aryloxy( $C_6-C_{10})$ aryl,  $(C_1-C_6)$ alkyl( $C_5-C_9$ )heteroaryloxy( $C_6-C_{10})$ aryl,  $(C_1-C_6)$ alkyl( $C_6-C_{10})$ aryloxy( $C_5-C_9$ )heteroaryl,   
 5  $(C_1-C_6)$ alkoxy( $C_6-C_{10})$ aryloxy( $C_6-C_{10})$ aryl,  $(C_1-C_6)$ alkoxy( $C_5-C_9$ )heteroaryloxy( $C_6-C_{10})$ aryl or  $(C_1-C_6)$ alkoxy( $C_6-C_{10})$ aryloxy( $C_5-C_9$ )heteroaryl wherein each aryl group is optionally substituted by fluoro, chloro, bromo,  $(C_1-C_6)$ alkyl,  $(C_1-C_6)$ alkoxy or perfluoro( $C_1-C_3$ )alkyl.

2. A compound according to claim 1, wherein n is 2.

3. A compound according to claim 1, wherein X and Y are both CR<sup>1</sup>  
 10 wherein R<sup>1</sup> is hydrogen.

4. A compound according to claim 1, wherein Ar is  $(C_1-C_6)$ alkoxy( $C_6-C_{10})$ aryl,  $(C_6-C_{10})$ aryl( $C_1-C_6$ )alkoxy( $C_6-C_{10})$ aryl, 4-fluorophenoxy( $C_6-C_{10})$ aryl, 4-fluorobenzyloxy( $C_6-C_{10})$ aryl or  $(C_1-C_6)$ alkyl( $C_6-C_{10})$ aryloxy( $C_6-C_{10})$ aryl.

5. A compound according to claim 1, wherein n is 2, X and Y are both CR<sup>1</sup>  
 15 wherein R<sup>1</sup> is hydrogen and Ar is  $(C_1-C_6)$ alkoxy( $C_6-C_{10})$ aryl,  $(C_6-C_{10})$ aryl( $C_1-C_6$ )alkoxy( $C_6-C_{10})$ aryl, 4-fluorophenoxy( $C_6-C_{10})$ aryl, 4-fluorobenzyloxy( $C_6-C_{10})$ aryl or  $(C_1-C_6)$ alkyl( $C_6-C_{10})$ aryloxy( $C_6-C_{10})$ aryl.

6. A pharmaceutical composition for (a) the treatment of a condition selected from the group consisting of arthritis, cancer, tissue ulceration, mucular  
 20 degeneration, restenosis, periodontal disease, epidermolysis bullosa, scleritis, in combination with standard NSAID'S and analgesics and in combination with cytotoxic anticancer agents, and other diseases characterized by matrix metalloproteinase activity, AIDS, sepsis, septic shock and other diseases involving the production of tumor necrosis factor (TNF) or (b) the inhibition of matrix metalloproteinases or the  
 25 production of tumor necrosis factor (TNF) in a mammal, including a human, comprising an amount of a compound of claim 1 effective in such treatment and a pharmaceutically acceptable carrier.

7. A method for the inhibition of (a) matrix metalloproteinases or (b) the production of tumor necrosis factor (TNF) in a mammal, including a human, comprising  
 30 administering to said mammal an effective amount of a compound of claim 1.

8. A method for treating a condition selected from the group consisting of arthritis, cancer, tissue ulceration, macular degeneration, restenosis, periodontal disease, epidermolysis bullosa, scleritis, compounds of formula I may be used in

-21-

combination with standard NSAID'S and analgesics and in combination with cytotoxic anticancer agents, and other diseases characterized by matrix metalloproteinase activity, AIDS, sepsis, septic shock and other diseases involving the production of tumor necrosis factor (TNF) in a mammal, including a human, comprising administering

5 to said mammal an amount of a compound of claim 1, effective in treating such a condition.

# INTERNATIONAL SEARCH REPORT

International Application No

PCT/IB 97/01582

**A. CLASSIFICATION OF SUBJECT MATTER**  
IPC 6 C07D493/08 A61K31/34

According to International Patent Classification (IPC) or to both national classification and IPC

**B. FIELDS SEARCHED**

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP 0 453 960 A (SHIONOGI & CO) 30 October 1991 see abstract; claims; example 3 ---	1-8
A	EP 0 606 046 A (CIBA GEIGY AG) 13 July 1994 see abstract; claim 2; example 6 ---	1-8
P, A	EP 0 780 386 A (HOFFMANN LA ROCHE ; AGOURON PHARMA (US)) 25 June 1997 see trans- N-hydroxy-2- (4-methoxyphenyl)-sulfonyl- cyclopentanecarboxamide see abstract; claims --- -/-	1-8

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

\* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search

17 March 1998

Date of mailing of the international search report

07. 04. 98

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2  
NL - 2280 HV Rijswijk  
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,  
Fax: (+31-70) 340-3016

Authorized officer

Paisdor, B



# INTERNATIONAL SEARCH REPORT

International Application No

PCT/IB 97/01582

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	<p>M.A. STOLBERG ET AL.: "Synthesis of a Series of Vicinally Substituted Hydroxamic Acids"</p> <p>JOURNAL OF THE AMERICAN CHEMICAL SOCIETY, vol. 79, 20 May 1957, DC US, pages 2615-2617, XP002059123</p> <p>see page 2615, column 2</p> <p>see page 2617, column 2, paragraph 2</p> <p>-----</p>	1-5

# INTERNATIONAL SEARCH REPORT

International application No.

PCT/IB 97/ 01582

## Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:  
because they relate to subject matter not required to be searched by this Authority, namely:  
Remark: Although claims 7 and 8  
are directed to a method of treatment of the human/animal  
body, the search has been carried out and based on the alleged  
effects of the compound/composition.
2. ☐ Claims Nos.:  
because they relate to parts of the International Application that do not comply with the prescribed requirements to such  
an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

## Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all  
searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment  
of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report  
covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is  
restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

# INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/IB 97/01582

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 0453960 A	30-10-91	AT 116650 T	15-01-95
		CA 2040319 A,C	20-10-91
		DE 69106425 D	16-02-95
		DE 69106425 T	04-05-95
		ES 2069112 T	01-05-95
		HU 210687 B	28-06-95
		JP 4211642 A	03-08-92
		KR 9702488 B	05-03-97
		US 5137914 A	11-08-92
EP 0606046 A	13-07-94	US 5455258 A	03-10-95
		AT 159012 T	15-10-97
		AU 684255 B	11-12-97
		AU 5265593 A	04-05-95
		CA 2112779 A	07-07-94
		DE 69314456 D	13-11-97
		DE 69314456 T	26-02-98
		FI 940012 A	07-07-94
		HU 70536 A	30-10-95
		JP 6256293 A	13-09-94
		MX 9400276 A	29-07-94
		NO 940038 A,B,	07-07-94
		NZ 250517 A	26-10-95
		US 5506242 A	09-04-96
		US 5552419 A	03-09-96
		US 5646167 A	08-07-97
		US 5672615 A	30-09-97
		ZA 9400048 A	11-08-94
EP 0780386 A	25-06-97	AU 7548296 A	31-07-97
		CA 2193178 A	21-06-97
		JP 9249638 A	22-09-97
		NO 965413 A	23-06-97
		PL 317604 A	23-06-97